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Review

MYO-MRI diagnostic protocols in genetic myopathies

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Abstract

Whole-body magnetic resonance imaging has emerged as a useful imaging tool in diagnosing and characterizing the progression of myopathies and muscular dystrophies. Whole-body MRI indications and diagnostic efficacy are becoming better defined with the increasing number of cases, publications and discussions within multidisciplinary working groups. Advanced Whole-body MRI protocols are rapid, lower cost, and well-tolerated by patients. Accurate interpretation of muscle Whole-body MRI requires a detailed knowledge of muscle anatomy and differential pattern of involvement in muscle diseases. With the surge in recently identified novel genetic myopathies, Whole-body MRI will become increasingly useful for phenotypic validation of genetic variants of unknown significance. In addition, Whole-body MRI will be progressively used as a biomarker for disease progression and quantify response to therapy with the emergence of novel disease modifying treatments. This review outlines Whole-body MRI indications and updates refined protocols and provides a comprehensive overview of the diagnostic utility and suggested methodology of Whole-body MRI for pediatric and adult patients with muscle diseases.

Keywords: Magnetic resonance imaging; Whole-body MRI; Inherited myopathy; Limb girdle muscular dystrophy; Congenital myopathy; Inflammatory myopathy.

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1. Introduction

Identifying the accurate diagnosis for patients with genetic and inflammatory myopathies is difficult given the clinical and genetic heterogeneity. In the quest for a definitive diagnosis, clinical evaluation, muscle enzymes (creatine kinase, CK), electrodiagnostic testing and muscle biopsy often lack specificity to limit the diagnostic odyssey [1]. Muscle MRI is emerging as a useful tool in the diagnosis and follow-up of patients with muscle diseases. Muscle MRI is a non-invasive tool to assess skeletal muscle edema or fibroadipose tissue transformation to assist with diagnosis, monitor disease progression, and guide muscle biopsy [2].

The initial use of MRI dates back more than 20 years and permitted only limited and segmental studies with a slow rate of image acquisition. However, even early studies demonstrated the superiority of MRI compared to CT for the detection of early intramuscular changes and advanced the description of patterns of certain diseases [3–11]. Muscle imaging pattern analysis is beginning to guide the selection of the appropriate genetic variants, thus leading to less muscle biopsies to lower the cost and invasiveness of the diagnostic path for patients [13]. MRI pattern analysis may distinguish pathogenic variants from rare but benign polymorphisms in the context of the vast quantity of sequencing data generated with next generation sequencing. Rather than simply prospectively identifying particular genes for Sanger sequencing, muscle MRI is increasingly being used retrospectively to guide the interpretation of genetic variants of uncertain significance identified by large gene panels or exome/genome sequencing [12]. MRI sequences measure atrophy, fatty transformation (T1 or Dixon sequences) and edema (T2 or STIR, IDEAL T2) for patients with suspected myopathies [14]. MRI can also identify loss of muscle bulk (atrophy) or muscle enlargement, either by true hypertrophy (adaptive hypertrophy) or fat replacement within the muscle, termed ‘pseudohypertrophy’ [15].

The aim of this review is to provide a comprehensive overview of the diagnostic utility and suggested methodology of Whole-body MRI (WBMRI) in hereditary and acquired myopathies by the MYO-MRI group. The MYO-MRI consortium was launched as a project funded by the European Cooperation in Science and Technology (COST, BM1304) to provide “Applications of MR imaging and spectroscopy techniques in neuromuscular disease: collaboration on outcome measures and pattern recognition for diagnostics and therapy development.” (https://www.cost.eu/actions/BM1304/).

1.2. Whole-body MRI

Although early studies focused primarily on lower extremity musculature, WBMRI can evaluate most muscle groups. Muscle MRI permits 1) a more widespread assessment of individual muscles thus allowing identification of disease patterns to increase diagnostic utility [16,17]; 2) monitoring natural history and disease progression [18,19]; 3) quantification of response to treatment [20]. WBMRI costs are similar to segmental imaging (cervical, lumbosacral etc.) as there are only a few images obtained for each region [21]. WBMRI is easily administered without radiation and can serve as an imaging biomarker that can be performed in less than one hour. In addition, WBMRI is sensitive to slowly progressive changes in muscle pathology and could deepen our understanding of the disease and progression as well as facilitate quicker clinical trials with smaller sample sizes [22].

1.3. Alternate imaging techniques

The main shortcomings of patient MRI include the need for sedation in young children, claustrophobic patients or patients carrying MR-incompatible devices, such as implantable cardioverter-defibrillator units. In addition, the necessary dedicated protocols and software or coils are limited in some centers [23]. Computer Tomography scans are useful if MRI is contraindicated, such if the patient has a non-MR compatible cardiac pacemaker or electronic device, or severe claustrophobia [24]. CT techniques should be used with caution in children with myopathies already undergoing a high number of radiating scans with spinal/orthopedic deformities and respiratory complications [25,26]. Muscle ultrasound (US) can demonstrate replacement of muscle tissue by fat and fibrous tissue with increased echogenicity [25,26]. Advantages of muscle US include its rapid bedside assessment, ability to identify and capture fasciculations, and lack of ionizing radiation, which is practical for pediatric patients and patients who cannot lie still without sedation [15,27]. However, high resolution US is limited to superficial muscle groups, whereas deeper muscle group studies are performed with lower frequency probes that decrease image resolution. MRI allows visualization of both superficial and deep muscles, can capture a wide field of view and is not as operator dependent as US [28–30]. Given limitations of CT and US, MRI has become the preferred imaging modality for superior soft tissue contrast and can image larger regions [31].

2. Muscle MRI protocol

2.1. MRI equipment prerequisites

WBMRI allows the assessment of large regions that are not typically imaged using standard MRI protocols or other imaging modalities. The field of study should span from the temporalis muscle in the head to the small intrinsic muscles of the feet. Most MRI machines will permit WBMRI via contiguous axial sections extending from head to toe and coronal sections from the anterior to the posterior surface of the body [1]. For older systems, WBMRI can be performed with a body coil integrated in the machine. In more advanced systems, imaging occurs from a network of surface coils, coupled with a posterior antenna integrated in the MRI table

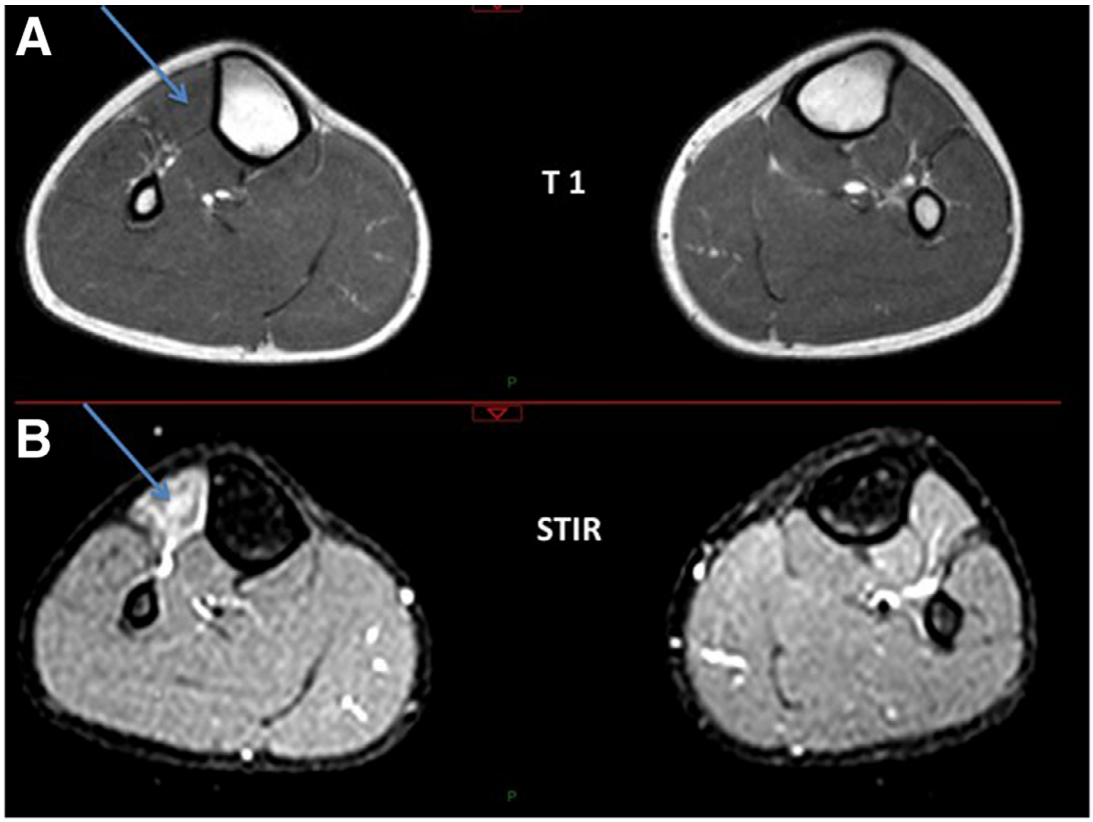

Fig. 1. demonstrates lower leg MRI images obtained in 2 standard sequences in early stage of FSHD. Typical images obtained in 2 separate sequences not simultaneously acquired, T1 usually can demonstrate fat replacement and dystrophic changes, and is normal in Fig. 1A. Fig. 1B demonstrates that the right tibialis anterior is hyperintense reflecting increase water content/edema indicating early myopathic changes.

for the thorax and abdomen, and lower limb antennas and surface antennas for assessing the upper extremities. Newer protocols of WBMRI include arms, forearms and hands in each study and consequently, the transverse view must permit a field of view (FOV) of 50 cm. For the pediatric population, especially for children shorter than 120 cm, most MRI systems permit adequate limb assessments.

2.2. WBMRI techniques

WBMRI techniques permit adequate spatial resolution to provide a detailed assessment of affected as well as preserved muscles. T1-weighted sequences (T1W) (Fig. 1) or fat images of 3-point Dixon (Fig. 2) or other in–out sequences permit a basic assessment of muscle volume and assess fatty tissue replacement in muscle. T2 weighted images with fat saturation and short tau inversion recovery (STIR) images complement T1 imaging by assessing early inflammation and edema and the evolution of muscle lesions (Fig. 1). To reduce acquisition time, "IDEAL T2" by General Electric (GE) protocols have been developed with in-out T2 weighted sequences within the same image sequence in the same stack, with fat and water images comparable to STIR sequences with better resolution (Fig. 3).

Protocols require sufficient spatial resolution to detect subtle fatty replacement of muscle tissue in early stages of disease. For smaller anatomical structures, such as with pediatric patients, higher resolution is required. For example, the distal leg of an affected child with a myopathy requires a superior resolution than the thigh of an adult [1,16,32] (Fig. 4). The challenge between acquisition time and quality of images requires WBMRI to be protocoled by experienced radiologists and technicians.

The axial plane remains the MRI reference plane of assessment for T1 weighted or fat saturated images as well as for T2 fat saturated images. Comparing T1 and T2 weighted images acquired in different planes, thicknesses or locations is difficult. If the patient's condition and the MRI machine time allows, a frontal plane of study can be performed. The frontal plane can better assess spinal deformities and certain muscle groups, in particular in the head (tongue, masticators) and pelvis [1,32]. The coronal examination uses three dimensional (3D) T1 weighted sequences to allow multiplanar reconstructions (Fig. 5). Such reconstructions are useful when there is suboptimal patient positioning due to disability or deformities to establish normal symmetry and anatomy important for muscle analysis. The 3D study also allows muscle volume measurements.

Studies in the axial plane and in the coronal plane will be divided into levels or "stacks" of exploration (Fig. 6). These levels are grouped for continuous scrolling in the axial plane and for a full-body frontal reconstructed image in the coronal plane. In thoracic and abdominal levels, image acquisition will be divided into coordinated breathing and controlled apneas

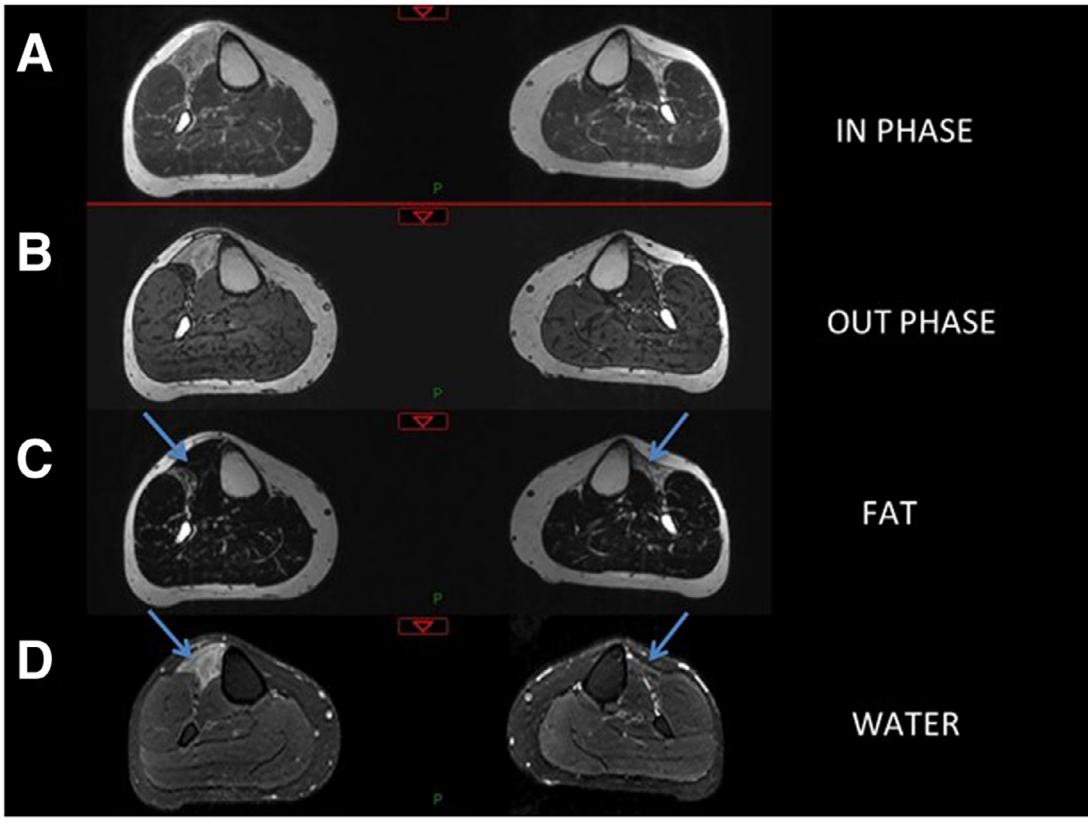

Fig. 2. demonstrates T2 Dixon based sequence of the lower leg in a patient with FSHD. Asymmetry noted earlier in disease, with shorter lived inflammatory period. All the several weighted images of the sequence were obtained at the same acquisition period, including In phase (Figure A), Outphase (Figure B), Fat which could be compared to T1 weighted images (Figure C) and Water (Figure D). Water images give T2 fat/sat weighting like STIR in Fig. 1B that demonstrates active muscle damage. Figure D demonstrates edematous right tibialis anterior, with atrophy of the left tibialis anterior, which is no longer edematous.

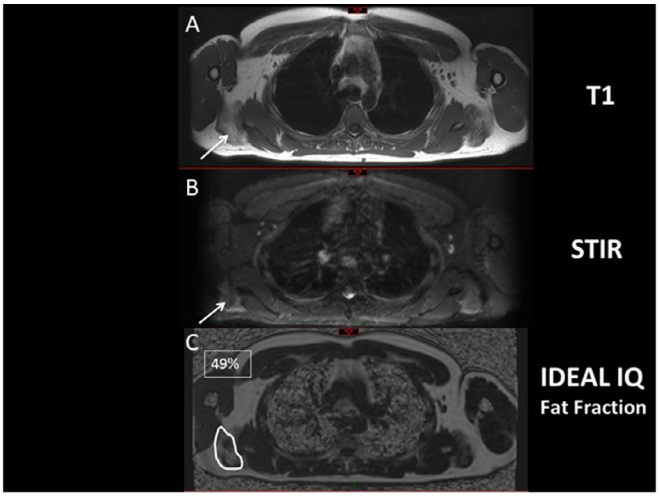

Fig. 3. Axial MR Images of thoracic region in patient with Pompe disease. Figure A. T1W images demonstrating mild symmetric fatty replacement changes in Teres major. Figure B. STIR Images again demonstrating mild hyperintensity in Teres Major. Figure C. Fat Fraction in Dixon demonstrating 49% replacement of fat in Teres major.

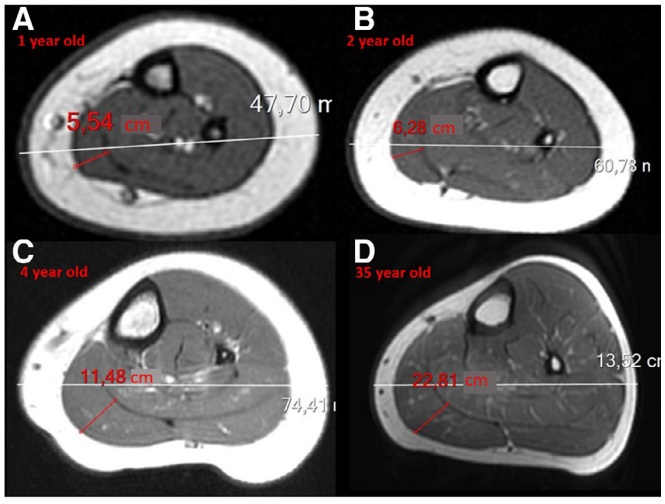

Fig. 4. demonstrating importance of resolution changes in children at different ages at the level of the lower leg. Fig. 6A–D demonstrates increasing limb size diameter. Fig. 6A requires a higher resolution given the smaller diameter. Fig. 6A-C demonstrates that due to smaller muscles in children, there needs to be an increase in spatial resolution of images to identify subtle changes in muscle, particularly important in children.

if tolerated by the patient. This allows images free of artifacts from respiratory movements.

In addition to the appropriate equipment and protocols, the imaging team requires experience managing adults and children with neuromuscular disease, who can have significant disability, with respiratory and/or cardiac failure [1,21,32,33]. For patients with respiratory failure, MRI should only be

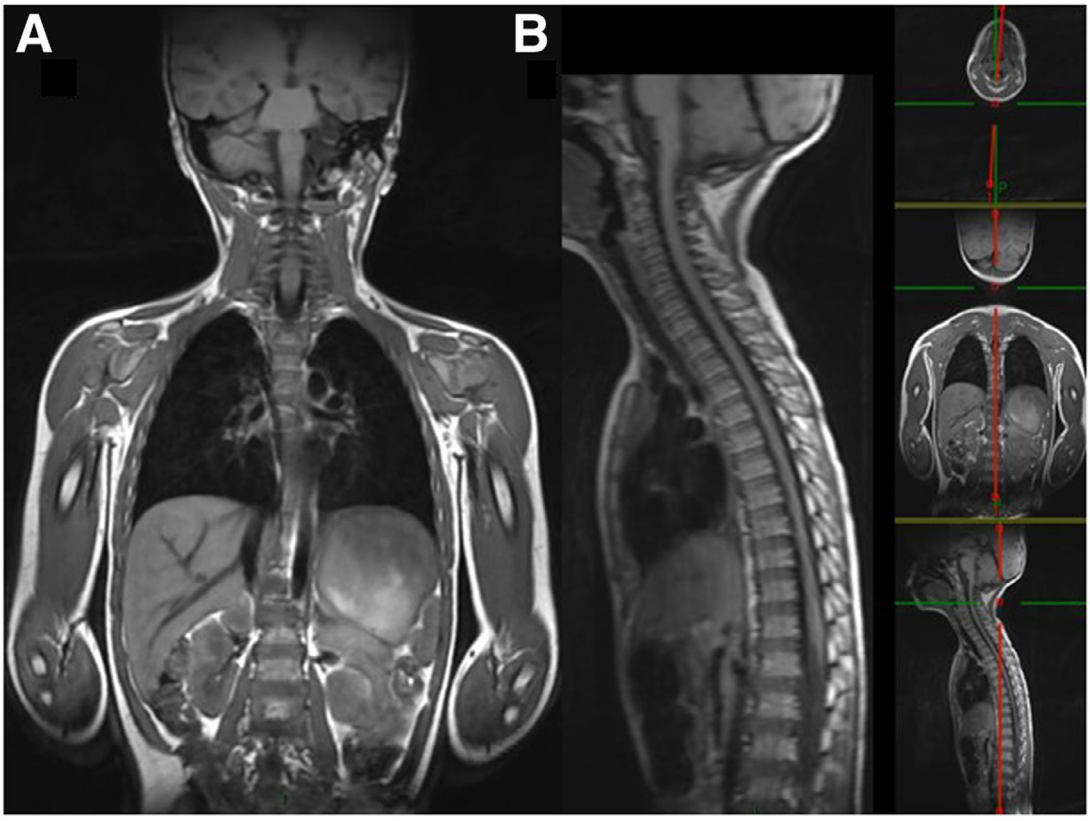

Fig. 5. demonstrates 3D images reconstruction. With 3D T1 (cube T1) coronal images in Figure A, multiplanar reconstruction in saggital view (Figure B) can be obtained.

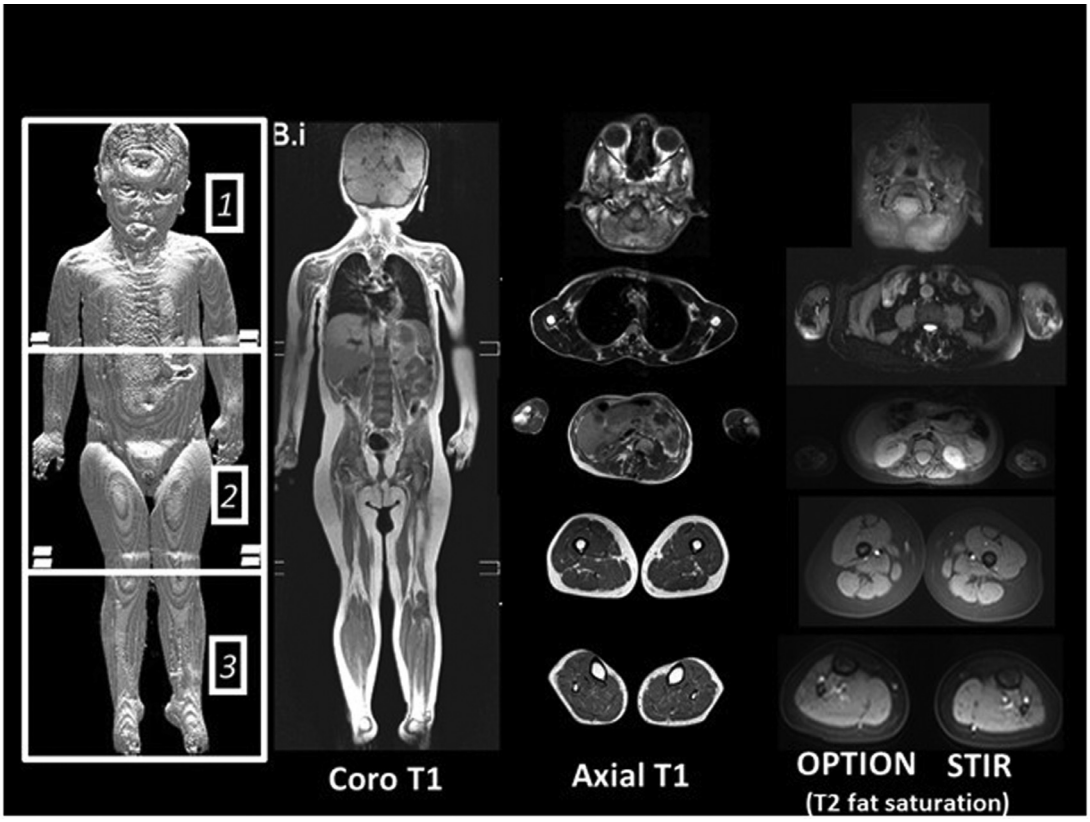

Fig. 6. demonstrating WBMRI acquired in blocks (“stacks”). Three stacks of images obtained Coronal B and Axial C planes as well additional axial T2 fat saturation STIR images in a child with DNM2 mutations and minimal fatty replacement, predominantly in hamstrings.

considered in institutions equipped with ventilation and non-magnetic monitoring equipment. Also, medical resuscitation or anesthesia teams should be in close proximity for the transport and surveillance of unstable patients during imaging [33]. In MRI cores with larger tunnels, both the child and parent can be imaged simultaneously. A parent can accompany and reassure the child and decrease/eliminate sedation [1].

3. WBMRI interpretation

Muscle MRI interpretation requires a detailed knowledge of anatomy, as well as the pattern of muscle involvement, which can evolve differently as the disease progresses [24,34]. Importantly, for the same genetic disease, different mutations within the same gene can have discrete clinical and radiographic presentations. Assessing these patients in specialized NMD centres offers the most precise differential diagnosis [35]. The added value of the specialist radiologist must be emphasized, both as a guarantor of accurate technical parameters and providing an exhaustive interpretation of the distribution of the disease and non-neuromuscular findings.

3.1. T1 weighted sequences

MRI techniques assess the loss of muscle bulk and fatty involution or replacement with connective tissue that largely represents irreversible damage. Fat appears hyperintense on T1 weighted images, while edema appears as low signal. WBMRI interpretation for T1W sequences are best interpreted in the axial and coronal planes.

Acquisition of T1W sequences are important for the assessment of the following muscle disorders:

- **Intramuscular fatty replacement.**
  T1W images demonstrate destruction of muscle fibers replaced by fat and the perimuscular fascia remains visible. On T1W images, fat appears hyperintense compared to edema, which appears hypointense (Fig. 1). The degree of fat replacement is estimated semi-quantitatively muscle by muscle from the region of the masticatory muscles to the toes with the Mercuri classification. It is an adaptation in MRI of the CT classification of Goutallier and Bernageau allowing to estimate the degeneration of the shoulder rotators [36]. The Mercuri classification is divided into four stages [37]:
  - 1 = normal
  - 2 = fat replacement less than 30%
  - 3 = fat replacement ratio estimated between 30% and 60%
  - 4 = fat replacement in muscle is greater than 60%

  Intramuscular fat replacement may be highly localized and muscles may not uniformly be affected. This illustrates the importance of carrying out a comprehensive study of each muscle and not simply a cut at the level of the middle section, as was incorrectly previously advocated [38]. To categorize the degree of intramuscular fatty replacement according to Mercuri, the frontal plane is more useful than the axial plane for certain muscles [33].
  When fat images are acquired by the 3-point Dixon method or other in-out sequences are used, the qualitative analysis is comparable to those obtained with conventional T1 weighted studies and perhaps more sensitive for subtle fatty changes. Such sequences offer the opportunity to quantify the fat fraction for some selected muscles or for all muscles. Axial T1 weighted images could be replaced by the 3-point Dixon method or In-out combined fat and T2 fat suppressed images.
- **Distribution of the disease.**
  The distribution of involvement provides an important clue when determining diagnosis by MRI [17,39]. The pattern of affected muscle groups is identified and then characterized by anterior or posterior compartments, proximal/distal muscle groups and involvement within muscle groups (Fig. 7). However, there is still a lack of correlation between imaging and the molecular diagnosis in many pathologies and many larger case series are required to better define patterns of involvement in specific myopathies.
- **Muscle volume.**
  In response to muscle atrophy, neighboring muscles can adapt and may increase in volume. This is conventionally called compensatory or “adaptative” hypertrophy. Muscle volume may also be increased in association with fat replacement, termed pseudohypertrophy. There are no muscle volume reference values; it is mainly the regional disproportion as a function of age and sex that highlights individual muscle involvement [40]. Therefore, if the analysis focuses only on the degree of intramuscular fat replacement and not muscle volume or disproportion compared to muscles of the same region, it is possible to miss muscles affected in the overall description of patterns [33]. Extremes of body weight and normative age-related decline in muscle quality are not sufficiently recognized, which impacts the ability to use MRI to diagnose neuromuscular disease especially with older patients [41].
- **The symmetrical or asymmetrical pattern of involvement.**
  The symmetrical or asymmetrical character of muscle involvement can guide diagnosis. For example, the well-described asymmetric muscle involvement of facioscapulohumeral muscular dystrophy (FSHD) (Fig. 8), as well as some LGMD (i.e. anoctamin5-related LGMD/R12) [35].
- **Type of intramuscular disorganization or muscle texture.**
  In some genetic myopathies, intramuscular involvement reveals highly suggestive MR characteristics. For example, without fully established sensitivity and specificity, collagen VI pathologies demonstrate a "tigroid pattern" [42]. This pattern reveals the preservation of an intramuscular central band that can be demonstrated in almost all involved muscles, but with variable distribution

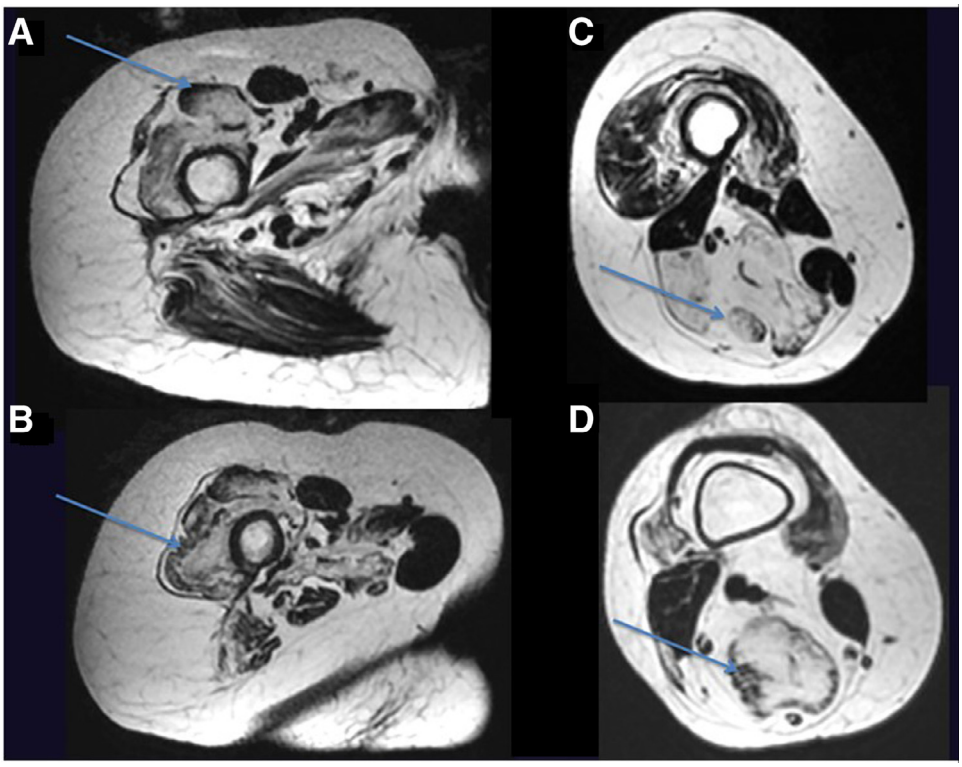

Fig. 7. demonstrates classic features of sarcoglycanopathy with identification of selectively affected/spared muscles and particularity of fatty replacement distribution. Figures A to D demonstrate a peripheral rim of preserved muscle, with more prominent central involvement (arrows) in rectus femoris (Figure A), vastus lateralis (Figure B), semitendonosis (Figure C) semimembranosis (Figure D).

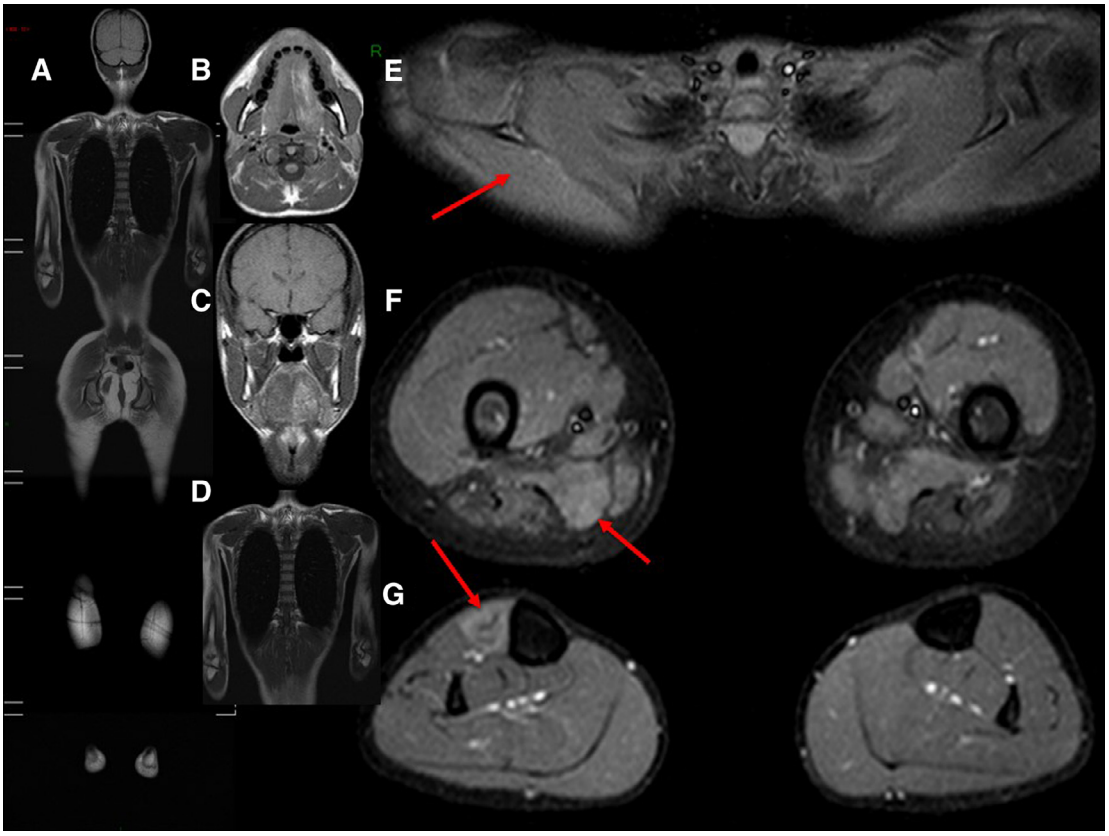

Fig. 8. demonstrating focal muscle involvement in FSHD and the importance of T2 weighted images with fat saturation use. Coronal (Figures A, C, D) and Axial (Figure B) MR images in patient with FSHD demonstrating typical muscle involvement of FSHD (Figure C) as well as focal, asymmetric and early muscle involvement (Figure F, G), which resemble an inflammatory myopathy.

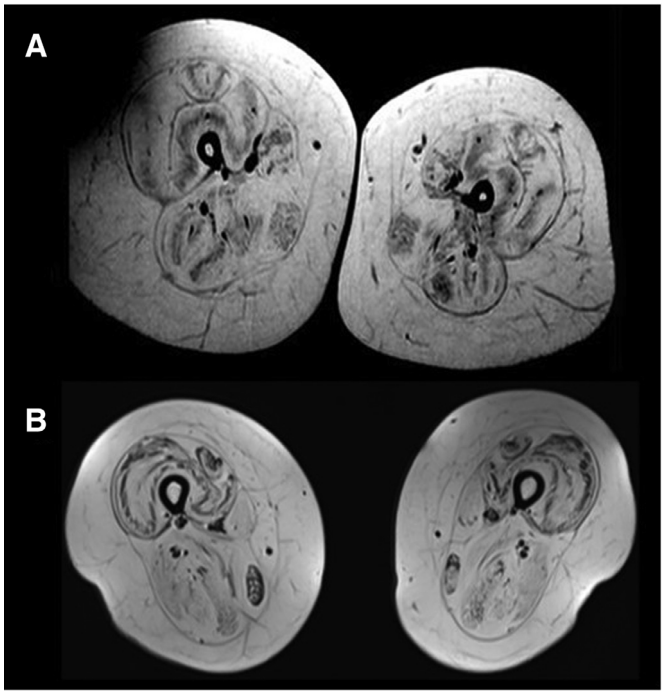

Fig. 9. demonstrating Tigroid pattern on muscle MRI. Axial T1 weighted images at the thigh demonstrating Tigroid patterns in Ullrich (*COL6*) myopathies (Figure A) and Calpainopathies (Figure B).

depending on the stage of disease evolution and severity [1,43] (Fig. 9).

- **Orthopedic involvement that may be associated with or impact neighboring muscles.**
  Orthopedic injuries should be considered in the analysis. Degenerative joint lesions are common and may be associated with decreased volume and intramuscular fatty replacement of the muscles involved in joint mobilization. When focal muscle changes affect one or only a very limited number of muscles and do not lead to a clear myopathic profile, consider a history of muscle injury (for example hamstring involvement in a football/soccer player). In children, ankylosis or a defect of joint development associated with the absence or abnormalities of neighboring muscles may demonstrate arthrogryposis [44]. In spondylarthropathy or in diffuse idiopathic skeletal hyperostosis (DISH) syndrome, the erector muscles could be totally replaced by fat due to immobility and not primary myopathy. For isolated paraspinal muscle involvement, an extrapyramidal disease such as parkinsonism needs to be considered. Finally, the neurological history can clarify when a selective pattern of muscle involvement could be attributable to lesions of the root or trunk, most often sequelae of a previous radiculopathy [45].

3.2. STIR or T2 sequences with fat saturation

STIR or T2 sequences with fat saturation sequences reveal an abnormal increase in the water content of muscles as demonstrated by high signal areas (Fig. 1). These changes are not specific and can represent inflammation (myositis), denervation (focal neuropathy), or an active injury in certain myopathies (ie. FSHD, dysferlinopathies, myotonic dystrophies, Pompe disease). These techniques can assess early phases of inflammatory muscle disease characterized by edema-like changes on fluid-sensitive MRI sequences (e.g. STIR), which can be followed by rapid fat replacement in muscular dystrophies (i.e. FSHD) or inflammatory myopathies [22,46]. The interpretation of the STIR sequences requires comparing T1-weighted images at the same level with the same slice thickness. In-out IDEAL T2 sequences also demonstrate diseased muscle with fat replacement areas with fat saturation that will have a very low signal and non-fat muscle areas can comparatively present with a relatively more pronounced signal. Adding IV gadolinium contrast is not routinely used as it increases scan time and does not provide additional information to STIR or T2-weighted images [47,48].

3.3. Dixon techniques

Dixon techniques represent a detailed chemical-shift imaging application producing water- and fat-only images from dual-echo acquisitions [49,50]. 3-point Dixon sequences (Fig. 2) provide better quantification of muscle content of water and fat per pixel [51]. The 3-point Dixon technique requires the acquisition of three gradient echo images at three different echo times. Typically, 3-point Dixon technique utilizes two acquisitions where the water and fat contributions are in phase and one acquisition where the water and fat contributions are out of phase [51]. This technique requires specialized software and a longer process of analysis than traditional T1-weighted images. However, Dixon results are more quantitative and provide improved reliability between centres that are necessary for natural history studies and clinical trials [24].

3.4. WBMRI technical interpretation

Radiologists require additional information about the results of other diagnostic clinical investigations and potential differential diagnoses for WBMRI interpretation (Clinical Information Sheet, Appendix 1). Without this, the differential diagnosis for the radiologist is too large and it is difficult to expect a precise diagnosis by imaging. The information on the affected muscles (fatty replacement, atrophy, high STIR signal) and preserved muscles can be grouped in a table with more than 100 muscles distributed in nine anatomical sub-regions (Table 1). From the distribution of affected or spared muscles, a diagnosis can be reached with a high probability in certain cases. In some patients, it is possible to rely on available decision trees, however many have previously focused on only lower limb involvement [52].

WBMRI can detect muscle disease as well as incidental findings without an obvious link to the muscular pathology, such as fractures or neoplastic changes [53,54]. The

Table 1
Assessment of muscle groups.

Name BD MRN Referring Physician Date		T1 Signal Quotation				T2 FS IHZ		STIR IHZ	
		Left	Comments Atrophy, Hypertrophy, Bands	Right	Comments Atrophy, Hypertrophy, Bands	Left	Right	Left	Right
	Muscle								
Face	Temporalis								
	Masseters								
	Pterygoid Med/Lat								
	Tongue								
Cervical/Neck	Sternocleidomastoids								
	Neck Extensor								
	Levator scapula								
	Longus colli								
Shoulder	Latissimus dorsi								
	Trapezius								
	Deltoid								
	Supraspinatus								
	Infraspinatus								
	Subscapularis								
	Pectoralis major/minor								
	Anterior serratus								
Arm	Anterior/Flexors								
	Posterior/Extensors								
Forearm	Flexor muscle group								
	Extensors muscle group								
Hand									
Thoracic Trunk	Intercostals								
	Thoracic Extensor								
Lumbar/Abdom	Lumbar Extensor								
	Psoas/ Iliac								
	Abdominal Muscles								
Pelvis	Gluteus maximum								
	Gluteus medius/min								
	Perineal Muscles								
	Adductor Longus/Magnus								
	Pectineus/Add Brevis								
	Ilio-Tibial band								
	Pectineus								
Thigh	Adductor longus								
	Quadriceps:								
	*Rectus femoris								
	*Vastus lateralis								
	*Vastus intermedius								
	*Vastus medialis								
	Sartorius								
	Gracilis								
	Hamstrings:								
	*Semimembranosus								
	*Semitendinosus								
	*Biceps femoris LH/SH								
Lower Leg/Calf	Gastrocnemius medialis								
	Gastrocnemius lateralis								
	Soleus								
	Tibialis anterior								
	Tibialis posterior								
	Extensor hallucis								
	Extensor digitorum longus								
	Peroneus muscles								
	Peroneus brevis								
	Flexor hallucis								
	Flexor digiti								
Foot	Extensor Digitorum Brevis								

Each muscle group can be staged as follows
1: Normal Appearance
2: Mild Involvement
3: Moderate Involvement
4: Severe Involvement

Increased Hypersignal Zones (IHZ)
1: Mild Intramuscular Hypersignal
2: Moderate Intramuscular Hypersignal
3: Severe Intramuscular Hypersignal

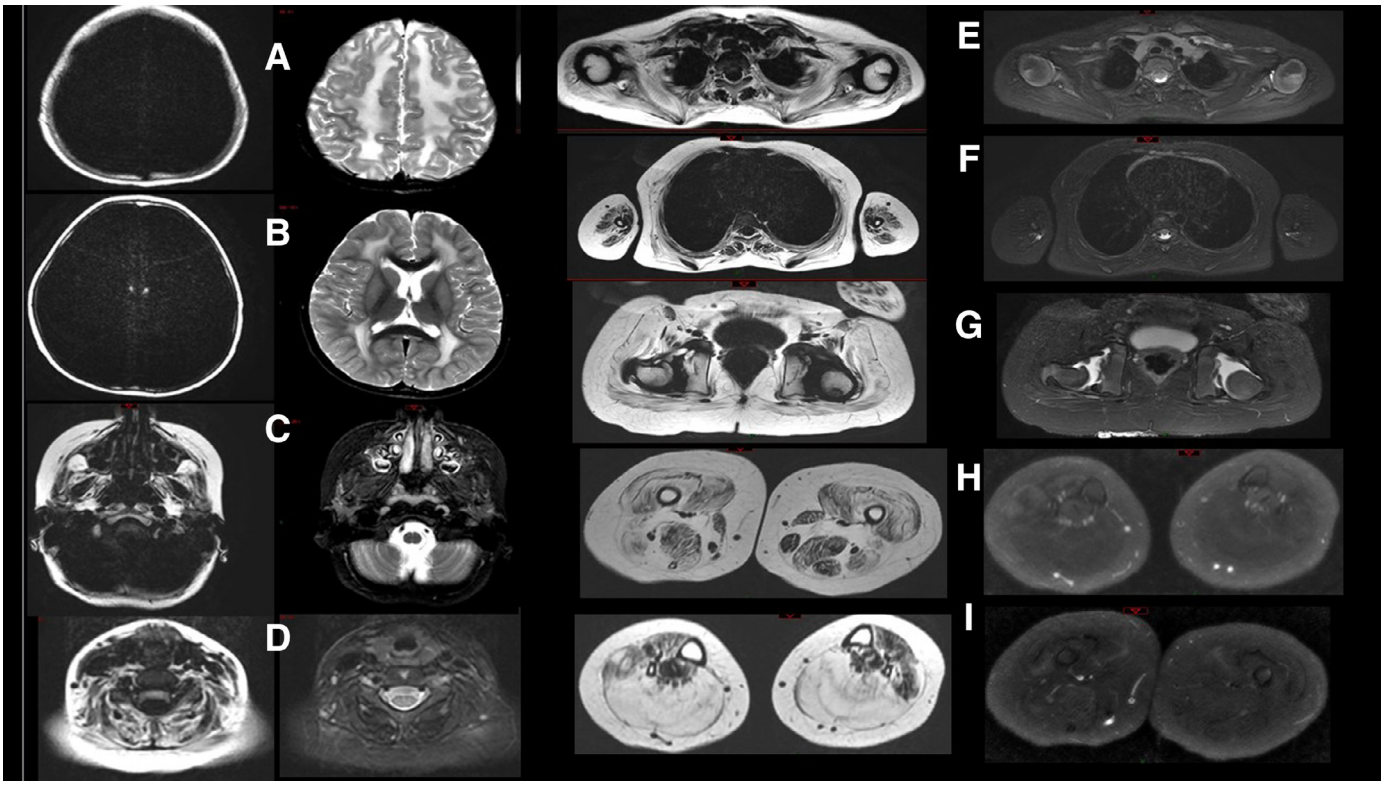

Fig. 10. demonstrating importance of "whole body" MRI, with axial IDEAL T2 sequence from head to toes in seven year old boy from North Africa with a presentation of congenital inherited muscular disorder associated with elbow, hip and knee severe deformities and retractions. The fat images are presented on the left and water images on the right at each level of the selection of nine of the 206 obtained images.
The diagnosis is made on the first stacks (Figures A–D) which revealed white matter diffuse high signal in the water image (T2 weighted with fat saturation) with sparing of the corpus callosum and internal capsule as previously described in LAMA 2. The muscle atrophy and fatty replacement is diffuse (Figures E-I). Fluid into the hip joints is easily detectable on G on bright signal in the water image (Figure G).

radiologist performing and interpreting the studies should report the possible extramuscular abnormalities region by region. In addition to whole-body exploration, MRI brain should be added in select patients with neurocognitive features to identify malformations, neuronal migration disorders or white matter lesions, more commonly associated with congenital muscular dystrophies. Some myopathies, such as *STIM-1* or *TRAPPC11*-related diseases affect not only the skeletal system but also thoracic/cardiac regions, abdominal organs, eyes, or the brain can be characterized by MRI to facilitate diagnosis [55,56].

4. Whole-body muscle MRI indications

Indications for WBMRI are rapidly expanding and can improve patient care by 1) facilitating diagnosis; 2) assessing the degree of progression and natural history; and 3) evaluating a therapeutic response:

4.1. WBMRI facilitates diagnosis

- **Myopathies with a clinical presentation demonstrating characteristic muscle MRI pattern**. The selective pattern of muscle involvement on WBMRI can in some cases point to the diagnosis of a specific genetic myopathy with novel imaging phenotypes. For example MRI patterns can differentiate between different muscular dystrophies with clinical phenotypic overlap, such as the rigid spine syndrome, which may be due to defects in a number of genes including *SEPN1, EDM, LMNA, COL6, LAMA2 and MYH7* (Fig. 10) [1,39,57,58]. WBMRI involvement can demonstrate sub-clinical muscle involvement and provide evidence of the pathogenicity of a genetic variant if not clinically apparent [13].
- **Undiagnosed clinically evident myopathy, particularly after negative muscle biopsy.** Muscle MRI can help target involved muscles to increase yield for a second biopsy, particularly in deep muscles. In patients with advanced or diffuse myopathies, MRI can identify less affected muscles (i.e. not totally replaced by fat) that may provide higher diagnostic yield in a biopsy [10,37]. Muscle US may be the initial tool for biopsy selection as US may be performed rapidly at the bedside and identify earlier edema than muscle MRI [59].
- WBMRI can assess for **non-neuromuscular involvement** in muscle disease that can facilitate diagnosis, such as identifying an underlying neoplastic process in dermatomyositis [60] (Fig. 11).

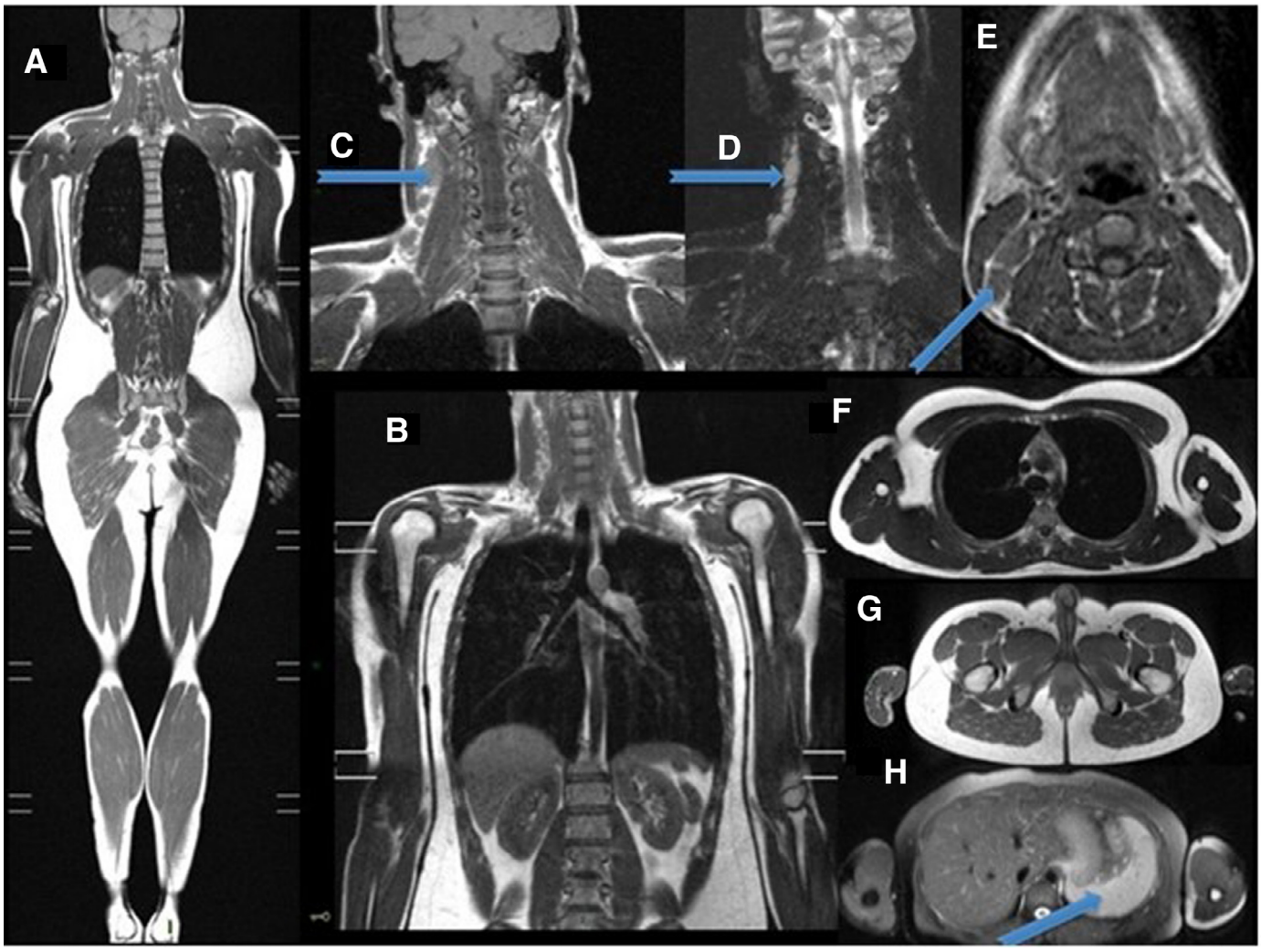

Fig. 11. demonstrating WBMRI can be essential to identify myopathy mimics. The MRI images of a patient referred for generalized weakness and hyperckemia demonstrate normal muscles (Figures A to H), with diffuse cervical lymphadenopathy (Figures C, D) and hypersplenia (Figures H). The diagnosis was Hodgkin lymphoma.

- **Suspicion of myopathy, without clear electromyogram findings or clear changes**. Muscle MRI has been used in certain cases to assess subclinical muscle involvement in patients presenting with hyperCKemia [61,62].
- **In childhood, adolescent or young onset myopathies when relatives or potential carriers need to be assessed**. Mild subclinical muscle abnormalities can be assessed in carriers or potentially affected family members to determine mode of genetic transmission.

4.2. WBMRI assesses degree of progression and natural history

- **Known genetic myopathies with no available treatment that require natural history data of progressive pattern of muscle involvement and rate of progression.** Fatty muscle infiltration observed in WBMRI can correlate with functional status and muscle strength of patients with myopathies. Graphic representation of muscle atrophy scoring such as heatmaps and machine learning analysis may identify key muscles to follow-up progression and investigate therapeutic effects [17,63]. Muscle MRI studies can detect involvement of muscle not identified by clinical manual strength testing [64,65].
- **Known, untreated myopathies to provide a baseline assessment** to assess distribution and severity of whole-body muscle involvement prior to initiation of treatment and assess treatment efficacy [66].

4.3. WBMRI evaluates therapeutic response

- **Known, treated inflammatory and genetic myopathies where progression in different muscle groups can be followed for a precise quantification of muscle degradation** [46,65].

5. Future directions

The number of newly diagnosed myopathies and the phenotypic variability of the known myopathies is constantly expanding. Although next generation sequencing is rapidly improving the diagnostic yield to identify inherited myopathies and muscular dystrophies, the sheer number of genetic variants of unknown significance identified in known myopathy genes often limits definitive diagnosis in more than half the patients [67–69]. The more common myopathies are slowly becoming well-characterized, however, the rare myopathies are still limited by lack of published MRI patterns of muscle involvement and muscles spared [34]. Interpretation of genetic variants of unknown significance will increasingly rely on WBMRI diagnostic patterns and will also help characterize novel myopathies.

Future publications of muscle MRI series of patients with known genetic myopathies need to identify a sufficient number of patients to 1) adequately cover the phenotypic range of the disease, 2) characterize disease evolution and 3) capture different presentations in relation to different mutations or variability in presentation with the same mutation [14,70,71]. International cohorts of neuromuscular imaging experts, such as MYO-MRI working groups, are being created to collectively assist in characterizing the pattern of involvement for rare myopathies. The MYO-MRI consortium is creating an online muscle MRI atlas, MYO-SHARE. MYO-SHARE is projected to contain thousands of anonymized MRI images of patients with genetically-confirmed myopathies to confirm diagnosis and provide an academic resource to share characteristic images with neuromuscular disease experts across the world. It will be important to next assess the value of MRI to determine the pathogenic variants in a prospective cohort undergoing comprehensive next generation sequencing screening [13], which can be facilitated with a larger patient cohorts in the MYO-MRI consortium.

MRI characterization of myopathies is difficult, not only because of the genotype-phenotype variability with myopathies, but also due to the progression in muscle sequences with variable patterns of progression in myopathies. Creating a gene-specific signature of muscle involvement on MRI is problematic given the large amount of data analysis required per patient [15]. “Heat maps” are being used to highlight the muscle involved and spared in a visually easily interpretable graphic fashion. “Regional” heat maps demonstrate specific muscle involvement and provide a diagnostic fingerprint of the disease, whereas there are hierarchical heatmaps which identify commonly and severely muscles are affected (positive diagnostic pattern) as compared to muscles preserved late in the disease (negative pattern) [17,39,72]. Muscle MRI heat maps will be increasingly utilized to display muscles affected in a consolidated graphic technique to allow visualization of a large amount of data to determine the pattern of muscle involved/spared, as well as progression of muscles (ie. muscles typically affected early vs late in the disease process) [15,39]. Future use of machine learning techniques will also permit more comprehensive data analysis to improve differential diagnosis, disease surveillance and response to therapies [63].

Finally, additional MRI sequences are being investigated to increase quantitative assessment of muscle involvement in genetic myopathies. For example, nuclear magnetic resonance (NMR) imaging elastography, late gadolinium enhancement and ultra-short TE (UTE) sequences are being investigated to evaluate skeletal muscle interstitial fibrosis [73]. MR Spectroscopy provides objective end-points with the measurement of the fat fraction made directly from the spectral peaks representing the lipids present in muscle [74]. Additional NMR possibilities exist to determine muscle perfusion and oxygenation and diffusion NMR as well as texture analysis algorithms permit additional data on muscle organization [73]. A recent report of the MYO-MRI Working Group 3 COST Action comprehensively highlights emerging muscle MR Imaging and Spectroscopy Techniques for Neuromuscular Disease [75].

6. Conclusions

WBMRI for patients with myopathies is becoming an important diagnostic standard to identify patterns of muscle involvement. Larger cohorts of patients are needed to accurately assess the natural history of the disease and the range of phenotypic variability. Like clinical and histopathological assessments, high level of expertise is needed to perform precise and sensitive examinations with a possible combination of qualitative and quantitative analysis to identify muscle MRI patterns that, in many cases, are not pathognomonic of a single disease. Given the relative rarity of these diseases and small numbers of patients per center, collaboration between different international MRI study groups is necessary to increase the number of patients analyzed through imaging platforms such as the MYO-MRI ‘MYO-SHARE.’

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Appendix 1. Sample clinical information sheet

Clinical Subtype:

- ☐ Myopathy NYD
- ☐ Novel Gene
- ☐ Congenital Myopathy
  - ☐ Central Core
  - ☐ Centronuclear
  - ☐ Nemaline
  - ☐ Other _____
- ☐ Congenital Muscular Dystrophy
  - ☐ CMD Subtype _____
- ☐ Myofibrillar Myopathy
- ☐ Distal Myopathy Type _____
- ☐ Duchenne Muscular Dystrophy
- ☐ Becker Muscular Dystrophy
- ☐ Limb Girdle Muscular Dystrophy
  - ☐ LGMD subtype _____
- ☐ Collagen 6 Myopathy
  - ☐ Ullrich
  - ☐ Bethlem
- ☐ Myotonic Dystrophy Type 1 ☐ 2 ☐
- ☐ FSHD
- ☐ OPMD
- ☐ Metabolic Myopathy
  - ☐ Metabolic Subtype _____
- ☐ Axial Myopathy
  - ☐ Head Drop
  - ☐ Camptocormia
- ☐ Inflammatory Myopathy
  - ☐ Necrotizing Myopathy _____
  - ☐ Dermatomyositis
  - ☐ Polymyositis
  - ☐ Inclusion Body Myositis
  - ☐ Other inflammatory myopathy

_____

Other myopathy:

Additional Clinical Information:

CK min _____ max_____

Biopsy Information:

Genetic Results:

Pattern of Weakness:

Family Members Affected (pedigree):

Age of Onset:

Age of Walking:

Cardiac Involvement: Yes / No

Respiratory Involvement: Yes / No

NCS/EMG:

Cognitive impairment: Yes / No

Scoliosis: Yes / No

Contractures: Yes / No

Additional Clinical Features:

Evolution/Disease Progression:

Current Treatment:

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